Despite advances in reproductive endocrine techniques as well as efforts to limit the number of embryos transferred, the incidence of multiple births in the United States has continued to increase. Data from the National Center for Health Statistics indicate that from 1971-1977 to 1998, the twin rate increased from 1.8% to 2.8%, and the rate of triplets increased 5.9-fold, quadruplets 11.0-fold, and quintuplets 5.3-fold.1 Similarly, the national trend toward an increase in preterm births (11.8% in 1999) is primarily the result of this increase in multiple births.

Multifetal pregnancy reduction (MPR) is a technique developed almost 15 years ago to decrease the incidence of preterm delivery in multiple gestations by reducing the number of live fetuses present in the uterus.2 In the first report by our center, complete pregnancy loss rates associated with this procedure were 33%. In 1993 we reported our experience with 200 completed cases of MPR, and the loss rate in that series had fallen to 9.5%.3 In our expanded series of 400 cases of MPR, the complete pregnancy loss rate had decreased to 8%.4 The improvement in outcomes with this procedure are thought to be largely due to increased operator experience as well as improvements in ultrasound equipment. Recently, Evans et al5 published their fourth report on the international collaborative experience with MPR. That study, comprised of data on 3513 cases collected from 11 centers in five countries (including our center), also documented the continued improved outcome over time.

The purpose of this series of 1000 consecutive cases of MPR performed at a single center is to further assess the outcome of this procedure and to assess trends over time.

**Material and methods**

A total of 1012 consecutive cases of MPR performed at the Mt Sinai Medical Center between the years of 1986 to 1999 constitute the study population. Because of the incomplete data in 12 cases, 1000 cases are included in this analysis, for a follow-up rate of 98.9%. All cases of MPR were performed for the indication of reducing fetal number. Cases in which a fetus was terminated because of a known anomaly (ie, selective termination) were not included in this analysis. All procedures were performed by
the transabdominal injection of potassium chloride into
the region of the fetal thorax under ultrasound guidance
and were performed by one of four operators (J. S., K. E.,
L. L., R. L. B.). Details relating to the technique of per-
forming the procedure have been reported previously.3
Since 1994, patients were offered chorionic villus sam-
ping (CVS) before MPR, and outcomes for this group
have been previously published.4 Data on pregnancy
outcome were collected in an ongoing fashion, and in-
formation entered into a specific MPR database with In-
ternational Review Board approval.

Complete pregnancy loss was defined as loss of the en-
tire pregnancy before 24 weeks' gestation. Unintended
pregnancy loss was defined as the spontaneous, nonelec-
tive loss of the entire pregnancy before 24 weeks' gesta-
tion. Trends over time were analyzed by dividing cases
into chronologic groups of 200. The gestational age (GA)
at loss was evaluated by categorizing it into 4-week inter-
vals after procedure. Mean GA of delivery was evaluated
for the entire study population and by the starting and
finishing numbers of fetuses. Rates of preterm births and
mean birth weights were also assessed by the starting and
finishing numbers.

Differences in proportions were evaluated by $\chi^2$
test, Mantel-Haenszel $\chi^2$ test for trend or two-tailed Fisher
test as appropriate.

**Results**

The number of MPRs annually performed at the Mt Sinai Medical Center has continued to increase, and 162
procedures were performed in the last year of the study. All procedures were performed between 9 and 13 weeks,
with 85.8% being performed between 11.0 and 12.9
weeks. Tables I and II demonstrate trends in starting and
finishing numbers over time. The majority of cases
started with three or four fetuses (84.3%) and finished
with two fetuses (86.4%). The proportion of cases start-
ing with triplets remained stable over time, whereas those
starting with quadruplets decreased slightly. There is a
trend toward an increase in cases starting with two fetuses
and finishing with one. Elective reduction to a singleton
was not offered until 1993, which corresponds to the 200
to 400 patient group in Table II.

Overall, 59 of the 1000 patients (5.9%) had a complete
pregnancy loss before 24 weeks. Five of these cases were
electively terminated, leaving an unintended loss rate of
5.4%. Indications for elective termination include hyper-
emesis, intrauterine growth restriction, oligohydramnios
in two cases, and the death of a spouse. The loss rate in
the initial 200 cases was 9.5%, and this fell to 6.0%, 5.0%,
4.5%, and 4.5% in the next 800 cases ($P = .04$, Fig 1).

Of the 54 unintended losses, only 8 (14.8%) occurred
within 4 weeks of the procedure, whereas 30 (55.6%)
were lost more than 8 weeks after MPR (Table III). There
were no significant differences in loss rate based on GA at
the time of the procedure ($P = .8$).

The loss rate was lowest in patients starting with twins
(2.5%) and highest for starting number of six or more
(12.9%). There was a trend toward an increase in loss
rates for starting number of six or more compared with
starting numbers of two to five (12.9% vs 5.2%, $P = .08$).
There were no statistically significant differences in loss
rates when comparing starting numbers of two, three,
four, or five fetuses (Table IV).

The difference in loss rate for finishing numbers of
one versus two (3.4% vs 5.5%) did not achieve statistical
significance because of the relatively small number of re-
ductions to a singleton. There was, however, a significant
increase in loss rate (16.7%, $P = .03$) for those finishing
with triplets (Table V).

Of the 1000 cases, 941 (94.1%) were delivered at 24 or
more weeks. Overall, the mean GA at delivery was 35.6
weeks (Table VI). The majority of patients (56.9%) were
delivered at a GA of 36 or more weeks, and only 32

---

### Table I. Percentage of cases based on starting numbers divided into chronologic groups of 200

<table>
<thead>
<tr>
<th>Starting No.</th>
<th>1-200</th>
<th>201-400</th>
<th>401-600</th>
<th>601-800</th>
<th>801-1000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0</td>
<td>1.0</td>
<td>3.5</td>
<td>6.5</td>
<td>9.0</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>44.0</td>
<td>52.5</td>
<td>62.5</td>
<td>57.5</td>
<td>58.0</td>
<td>54.9</td>
</tr>
<tr>
<td>4</td>
<td>44.5</td>
<td>33.0</td>
<td>29.5</td>
<td>26.0</td>
<td>20.0</td>
<td>29.4</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
<td>8.5</td>
<td>8.5</td>
<td>7.5</td>
<td>10.5</td>
<td>8.6</td>
</tr>
<tr>
<td>6+</td>
<td>3.5</td>
<td>5.0</td>
<td>2.0</td>
<td>2.5</td>
<td>2.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>

### Table II. Percentage of cases based on finishing numbers divided into chronologic groups of 200

<table>
<thead>
<tr>
<th>Finishing No.</th>
<th>1-200</th>
<th>201-400</th>
<th>401-600</th>
<th>601-800</th>
<th>801-1000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>7.5</td>
<td>15.0</td>
<td>15.0</td>
<td>18.5</td>
<td>11.8</td>
</tr>
<tr>
<td>2</td>
<td>94.5</td>
<td>89.5</td>
<td>83.0</td>
<td>84.0</td>
<td>81.0</td>
<td>86.4</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>3.0</td>
<td>2.0</td>
<td>1.0</td>
<td>0.5</td>
<td>1.8</td>
</tr>
</tbody>
</table>
(3.4%) were delivered between 24 and 28 weeks. Interestingly, no significant differences in this very early prematurity rate was seen with the starting numbers of three, four, five, or six or more fetuses. The best outcome was seen for the small number of patients (n = 39) starting with two fetuses. In this group, 92.3% delivered at 36 or more weeks.

Interestingly, although patients finishing with two or three fetuses were delivered on average at the same GA reported for nonreduced twins and triplets (ie, 35.3 and 33.5 weeks, respectively), those finishing with one fetus were delivered approximately 2 weeks earlier than anticipated for nonreduced singletons (Table VII). No patients ending with a singleton was delivered before 28 weeks, and only 4.5% were delivered before 32 weeks. Only 3.9% of the patients reduced to twins were delivered before 28 weeks, and more than half (53.4%) were delivered at 36 weeks or later. As expected, 26.7% of patients finishing with triplets were delivered before 32 weeks.

Analysis of mean birth weight by starting number demonstrates a linear decline in birth weight with increasing starting numbers (P < .0001, Fig 2).

Table III. Gestational age at unintended pregnancy loss

<table>
<thead>
<tr>
<th>Weeks after procedure</th>
<th>No. of losses (%)</th>
<th>Percent total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>8/54 (14.8%)</td>
<td>0.8</td>
</tr>
<tr>
<td>4-8</td>
<td>16/54 (29.6%)</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt;8</td>
<td>30/54 (55.6%)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table IV. Unintended loss rate by starting number

<table>
<thead>
<tr>
<th>Starting number (No.)</th>
<th>Unintended loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (40)</td>
<td>2.5</td>
</tr>
<tr>
<td>3 (549)</td>
<td>5.3</td>
</tr>
<tr>
<td>4 (294)</td>
<td>5.4</td>
</tr>
<tr>
<td>5 (86)</td>
<td>4.7</td>
</tr>
<tr>
<td>6+ (31)</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Table V. Intended loss rate by finishing number

<table>
<thead>
<tr>
<th>Finishing number (No.)</th>
<th>Loss rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (118)</td>
<td>3.4</td>
</tr>
<tr>
<td>2 (864)</td>
<td>5.5</td>
</tr>
<tr>
<td>3 (18)</td>
<td>16.7</td>
</tr>
</tbody>
</table>

* P = .03 for 1 or 2 vs 3

weeks, with a range of 15 to 28 weeks. In addition, three patients underwent subsequent selective termination of an abnormal fetus. There were 16 neonatal deaths, for a neonatal mortality rate of 0.9%. The majority of these deaths were due to severe prematurity, whereas two cases were attributed to birth asphyxia and a cardiac anomaly.

Comment

In this series of 1000 cases of MPR performed at a single institution, the number of procedures performed per year has continued to increase. Although the proportion of patients presenting with three fetuses has remained stable over time, we have seen a trend toward fewer quadruplets and more patients requesting a reduction from twins. Although the overwhelming majority of patients reduce to twins (86.4%), an increasing number are choosing reduction to a singleton. In the last 200 procedures reported in this series, almost 19% were reduced to a single fetus. Early in our experience a reduction to a singleton was only performed for medical indications, whereas later is was offered for purely elective indications.
The overall unintended complete pregnancy loss rate of 5.4% is the lowest reported by our center to date. In our experience, the steepest portion of the learning curve seems to have occurred during the first 200 cases, when the loss rate was 9.5%. Since that time, the loss rate has only varied from 4.5% to 6.0%. This differs from data published in the international multicenter collaborative series of over 3500 cases of MPR from 11 different centers.6 In that report, loss rates declined from 13.2% to 9.4% to 6.4% over a decade. This discrepancy may reflect the inherent differences of a multicenter experience versus that of a single center. The rapid learning curve at our institution is likely due to of the small number of operators performing the procedure as well as strict adherence to an established protocol. In addition, all procedures at our center were performed via the transabdominal approach, whereas the collaborative experience contains procedures performed transvaginally. This collaborative series documents a higher loss rate with transvaginal and transcervical procedures compared with those performed transabdominally (25.4% vs 8.5%, \( P < .0001 \)).6

It is interesting to consider that of the 5.4% of patients who underwent a complete pregnancy loss, more than half lost the pregnancy more than 2 months after the MPR procedure. Although it is nearly impossible to be certain whether those losses were due to the reduction procedure or are part of the background risk of pregnancy loss in this group, there are data to support the latter conclusion. Yaron et al9 evaluated triplet-to-twin reductions at Wayne State University and compared them with two large sets of nonreduced twins. The loss rate among the approximately 800 sets of nonreduced twins was 5.8% and 6.3% for the two groups, which is very similar to their triplet-to-twin loss rate, as well as the loss rate in our series. Because the majority of our patients were reduced to twins, our overall loss rate is largely due to the expected background losses. The loss rate of 0.8% in the first 4 weeks after procedure is similar to that associated with other needle-guided procedures (ie, amniocentesis, CVS) and may more accurately reflect the procedure-related risks of MPR. Furthermore, couples who consider the option of undergoing an MPR should also be aware of the background risk of pregnancy loss in nonreduced higher-order multiple gestations. The loss rate of 5.4% after MPR appears to be far less than that of nonreduced triplets. Data collected from 10 studies, including a total of 332 sets of nonreduced triplets, reported a complete pregnancy loss rate of 11%.10

This current series of 1000 cases confirms our previous finding that loss rates do not significantly differ based on starting numbers of two, three, four, or five fetuses.5 There was, however, a trend toward a 2-fold increased risk of loss with starting numbers of six or more fetuses. This differs from data from the collaborative series, which reported higher loss rates with increasing starting numbers of fetuses. Similarly, although Evans et al6 found that very premature delivery was correlated with the starting number, our data do not support this conclusion. The rate of very premature delivery was similar with starting numbers of three, four, five, or six or more fetuses and appeared to be lower in patients starting with twins.

Although loss rates did not vary with starting numbers of two to five fetuses, we did find a significant increase in loss rates with a finishing number of three. Because some patients with higher-order multiples are interested in reduction to triplets, this information needs to be incorporated into the counseling.

The overall mean GA of delivery in patients undergoing MPR was 35.6 weeks. Patients reduced to twins and triplets delivered at the same GA expected for nonreduced twins and triplets. Although this study does not provide a comparison group of nonreduced twins and

Table VI. Gestational age at birth according to starting number

<table>
<thead>
<tr>
<th>Starting No.</th>
<th>Mean (wk)</th>
<th>24-28 wk</th>
<th>28-32 wk</th>
<th>32-36 wk</th>
<th>36+ wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (n = 39)</td>
<td>38.1</td>
<td>0 (0%)</td>
<td>1 (2.6%)</td>
<td>2 (5.1%)</td>
<td>36 (92.3%)</td>
</tr>
<tr>
<td>3 (n = 515)</td>
<td>35.8</td>
<td>16 (3.1%)</td>
<td>40 (7.8%)</td>
<td>153 (29.2%)</td>
<td>306 (59.4%)</td>
</tr>
<tr>
<td>4 (n = 278)</td>
<td>35.3</td>
<td>10 (3.6%)</td>
<td>28 (10.1%)</td>
<td>90 (32.4%)</td>
<td>150 (54.0%)</td>
</tr>
<tr>
<td>5 (n = 82)</td>
<td>34.7</td>
<td>5 (6.1%)</td>
<td>8 (9.8%)</td>
<td>36 (43.9%)</td>
<td>33 (40.2%)</td>
</tr>
<tr>
<td>6+ (n = 27)</td>
<td>34.6</td>
<td>1 (3.7%)</td>
<td>3 (11.1%)</td>
<td>15 (48.2%)</td>
<td>10 (37.0%)</td>
</tr>
<tr>
<td>Total (n = 941)</td>
<td>35.6</td>
<td>32 (3.4%)</td>
<td>80 (8.5%)</td>
<td>294 (31.2%)</td>
<td>553 (56.9%)</td>
</tr>
</tbody>
</table>

Table VII. Gestational age at birth according to finishing numbers

<table>
<thead>
<tr>
<th>Finishing No.</th>
<th>Mean (wk)</th>
<th>24-28 wk</th>
<th>28-32 wk</th>
<th>32-36 wk</th>
<th>≥36 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 111)</td>
<td>37.9</td>
<td>0 (0%)</td>
<td>5 (4.5%)</td>
<td>9 (8.1%)</td>
<td>97 (87.4%)</td>
</tr>
<tr>
<td>2 (n = 815)</td>
<td>35.3</td>
<td>32 (3.9%)</td>
<td>71 (8.7%)</td>
<td>277 (34.0%)</td>
<td>435 (53.4%)</td>
</tr>
<tr>
<td>3 (n = 15)</td>
<td>33.5</td>
<td>0 (0%)</td>
<td>4 (26.7%)</td>
<td>8 (53.3%)</td>
<td>3 (20.0%)</td>
</tr>
</tbody>
</table>
triplets, the literature suggests that nonreduced twins and triplets are delivered at approximately 35.5 and 33.5 weeks.\textsuperscript{9,10} However, the mean GA of delivery of patients reduced to singletons was about 2 weeks earlier than that of nonreduced singletons.

Unlike our previous reports\textsuperscript{3,4} but consistent with other published series,\textsuperscript{6-8} birth weights were found to decrease with higher starting numbers. Although the exact pathophysiologic mechanisms underlying this phenomenon is uncertain, it has been suggested that there may be a fundamental “imprinting” of the uterus early in pregnancy that is not eliminated by an MPR.\textsuperscript{5}

In conclusion, this large series confirms the low risk of pregnancy loss associated with MPR and demonstrates that patients undergoing this procedure behave similarly to their nonreduced counterparts, both in terms of pregnancy loss and GA at delivery. Although the overwhelming majority of our patients have reduced to twins, we have noted a trend toward more reductions to singletons. Unlike previous reports documenting higher risks with reduction to singletons, in our experience this is associated with the lowest loss rates and lowest chances of preterm delivery.\textsuperscript{6,11} The increase in the elective reduction to a singleton seen in the last 200 cases may be due to the communication of this improved outcome to patients during initial consultation. Nevertheless, there are not enough data at this time to recommend that women opting for an MPR should be counseled to reduce to a singleton rather than twins.

\textbf{REFERENCES}